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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,956	03/15/2004	Akihide Fujimoto	89212.0017	2356
26/021 7590 03/13/2009 HOGAN & HARTSON LLP. 1999 AVENUE OF THE STARS SUITE 1400 LOS ANGELES, CA 90067				
EXAMINER				
POHNERT, STEVEN C				
ART UNIT		PAPER NUMBER		
1634				
MAIL DATE		DELIVERY MODE		
03/13/2009		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Attachment to Advisory**

**Continuation of box 3:** The amendments filed on 2/20/2009 have deleted the limitation of melanoma from claim 44 and has presented a newly amended claim 46 which previously depended from claim 44 without the limitation of melanoma as well. The deletion of melanoma from the claim was not done in compliance with 37 CFR 1.121 and thus is non-compliant. Further this amendment broadens the scope of the claims from those presented prior to Final rejection and thus would require further search and consideration.

**Continuation of box 11:**

The request for reconsideration has been considered but does not place the application in condition for allowance for the reasons of record in view of the non-entry of the after final amendment.

The amendment asserts that claims 35-37, 58-61, 87-88 and 91-92 have been amended to delete the coma in "interferon, alpha 2b." The examiner appreciates there appears to be a dash above the comma in the claims, but it is unclear if this is meant to be a deletion as claim 36 has the same dash above the comma between interferon and alpha-2b, but this is a new limitation added by amendment. The examiner suggests that deletion of the comma be denoted by double brackets as suggested by 37 CFR 1.121. Review of all the claims for the presence of the comma discussed would be appreciated in order to mitigate further objections due to this.

The response asserts that Soengas does not render the instant claims obvious as in figures 1b and 1C samples 6 and 16 have LOH at one position and have APAF-1

expression by in situ hybridization. The response further asserts that Soengas has mapped APAF-1 to a different position than the instant specification. It is noted the applicant elected the combination of all four markers recited in the response to restriction filed 8/14/2006. Thus based on the election the claims require the whole combination of markers and Soengas teaches that in subjects 4, 12, and 18 in which LOH was observed for all 4 markers there was no expression of APAF-1 as detected by in situ hybridization. Further interpretation of claim to require 2 demonstrates that loss of any two of the 4 markers is indicative of the inability to detect APAF-1, which Soengas teaches is indicative of disease progression. The arguments to LOH of APAF-1 are beyond the scope of the elected invention, as the claim requires the combination of the elected markers.

The response asserts that the combination of Soengas and Gocke do not render the instant claims 1-3, 6-8, 12-13, 74 and 81-81 obvious as neither teach detection of the elected markers in accellular DNA and accellular DNA analysis is unpredictable. This argument has been thoroughly reviewed but is not considered persuasive as Soengas teaches detection of the recited markers and Gocke teaches the use of accellular DNA for detection of disease. The arguments to the unpredictability of accellular DNA appears to be arguments of counsel not supported by evidence. First, MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding

unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding unpredictability of accellular DNA must be supported by evidence, not argument.

This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.

Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:

- (1) prior to a final rejection,
- (2) before appeal in an application not having a final rejection, or
- (3) after final rejection and submitted
  - (i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or
  - (ii) with a satisfactory showing under 37 CFR 1.116(b) or 37 CFR 1.195, or
  - (iii) under 37 CFR 1.129(a).

With respect to claims 35 and 58-59 applicant again argues the teachings of Soengas are drawn to APAF-1 negative cells while the instant invention is drawn to

detection of any of the four markers. Again the applicant is reminded the restriction response of 8/14/2006 elected the combination of all four markers. Further as addressed above the teachings of Soengas clearly demonstrates that deletion of at least two markers as well as the 4 elected is correlated with decreased expression of APAF-1 and indicates a low probability of response.

The response continues by asserting that the teachings of Soengas are in vitro and thus cannot render in vivo biochemotherapy as obvious. This is arguments of counsel that have not been supported by evidence. Based on the teachings of Soengas association of APAF-1 status with LOH of the elected combination of markers would render the instant claims obvious as Soengas teaches, "Assessment of APAF-1 status may therefore improve the therapeutic management of patients with malignant melanoma" (page 210, 2nd column, 1st paragraph).

The response asserts the teachings of Soengas to APAF-1 does not render the instant claims 44-45 obvious as the response asserts that Soengas does not teach detection of any one the markers with low probability of survival. Again the applicant is reminded the restriction response of 8/14/2006 elected the combination of all four markers. Soengas does suggest that LOH of the markers is indicative of decreased APAF-1 expression and thus indicative of progression and resistance to chemotherapy rendering the claims obvious. The response further asserts the teachings of Taback do not render the instant claims obvious. These arguments have been thoroughly reviewed but are not considered persuasive as the Soengas teaches the markers of he claims and Taback teaches LOH in blood as a prognostic indicator of metastatic

melanoma, thus in combination with the teachings of Soengas renders the instant claims obvious.

Applicants remaining arguments refer to the amended claims and rely solely on the amendments. The applicant provided no further arguments not already considered. Since the arguments were not entered, the arguments are moot. Therefore the arguments drawn to the after final amendments have not been considered.

### **Conclusions**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Steven Pohnert

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Primary Examiner, Art Unit 1634